REMARKS

Applicants have amended page 19 of the specification to correct a clerical error in which OE-HABP was listed instead of BM-HABP as being examined in human smooth muscle cells, fetal lung fibroblasts, umbilical vein endothelial cells and HL-60 and U937 cells. This error is evident upon reading the subsequent sentence, and in light of the paragraphs preceding and following the amended paragraph, all of which refer to BM-HABP rather than OE-HABP.

Additionally, the second full paragraph of page 20 has been amended to correct a clerical error regarding the degree of identity between the BM-HABP protein of the present invention and the TSG-6 protein of SEQ ID NO:12. In particular, the sequences are 31% identical overall, as determined using the computer program MegAlign, rather than 43% identical. *See* alignment and calculation submitted herewith as Exhibit A. Applicants note that this error apparently arose because an NCBI BLAST alignment of the two sequences shows that they are 43% identical over a 104 amino acid stretch (amino acids 52 to 155 of SEQ ID NO:11), as opposed to over the entire polypeptide. *See* alignment submitted herewith as Exhibit B. One of skill in the art would readily be able to determine the error in the percent identity between TSG-6 and BM-HABP by examining the sequence alignment in Figure 8.

Additionally, the paragraph bridging pages 34 and 35 of the specification has been amended to correct an obvious typographical error with respect to the correction of the NaCl and trisodium citrate concentrations for 5x SSC. 5x SSC is a component of many hybridization solutions and is well known in the art. (*See*, e.g., Exhibit D, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley and Sons, N.Y., at page 2.10.7 (1989)). SSC is normally made as a 20x stock solution, and then diluted accordingly for a particular use. Exhibit D shows that a 20x SSC stock solution contains 3 M NaCl and 0.3 M trisodium citrate. (*See*, e.g., Exhibit D, CURRENT PROTOCOLS, at page A.2.5.) To make a 5x SSC solution, the 20x solution must be diluted by a factor of four. Therefore, a 5x SSC solution contains 750 mM NaCl (3 M ÷ 4 = 750 mM) and 75 mM trisodium citrate (0.3 M ÷ 4 = 75 mM). One skilled in the art would have immediately recognized that the amounts of ingredients listed on page 34 in the specification for a 5x SSC solution were incorrect. Rather than describing a 5x SSC solution, made up of 750 mM NaCl and 75 mM trisodium citrate, the specification inaccurately listed the ingredient

amounts for a 1x solution. The skilled artisan, in recognizing the typographical error, could have easily adjusted the amount of ingredients described in the specification to properly make a 5x SSC solution.

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also the appropriate correction. *See*, M.P.E.P. § 2163.07. Here, the recognition of the typographical errors, along with the correction of the errors in the specification is obvious to one skilled in the art; therefore, the correction does not constitute new matter. Therefore, because no new matter will be added to the specification if these typographical errors are corrected, Applicants respectfully request that the amendments to the specification to recite BM-HABP instead of OE-HABP on page 19, to recite the correct percent identity between TSG-6 and SEQ ID NO:12 on page 20, and to recite the correct concentrations of sodium chloride and sodium citrate in 5x SSC on page 34 be entered.

Applicants have amended claims 31-32 and 36-37 to add the phrase "wherein said first polypeptide binds hyaluronan." Claims 41-44, 48-51, 55, and 72 have been amended to replace the term "comprising" with the phrase "consisting of." Claims 55-66, 68-75, and 77-80 have been amended to replace the term "protein" with the term "polypeptide." Additional minor amendments have been made to the wording of the claims for consistency and to correct grammar. Claims 67 and 76 have been canceled without prejudice or disclaimer.

A substitute sequence listing is submitted herewith. The sequence listing has been amended to correctly disclose the amino acid sequence of BM-HABP (SEQ ID NO:10 and SEQ ID NO:11) of the present invention, as shown in Figures 4A-B.

All of the above described amendments are fully supported by the specification, figures, and claims as originally filed, and thus no new matter has been added.

Claims 23-66, 68-75, and 77-80 are pending. Applicants respectfully request reconsideration of the rejections in view of the following remarks.

I. Rejections Under 35 U.S.C. § 101

The Examiner has maintained the rejection of claims 23-80 under 35 U.S.C. 101 because the invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. *See* Paper No. 21, pages 3-7. In particular, the Examiner asserts that "the specification fails to assert any utility for the claimed protein." *Id.* at page 3.

The Examiner also alleges that because two post-filing date proteins with higher homology to BM-HABP than TSG-6 have been identified, "the protein of SEQ ID NO:11 cannot be identified as a member of 'TSG-6 (HABP)' family. If the protein has similar activity, it would have indicated close sequence similarity with W84087." *Id.* at pages 3-4.

The Examiner further asserts that the specification does not provide "any biological activity of the polypeptide itself." *Id.* at page 4. Regarding the activities of BM-HABP described in the specification, the Examiner contends that "these activities are not demonstrated." *Id.* Finally, the Examiner alleges that "based on the specification it is unclear what activity the claimed proteins or protein fragments possess and therefore unclear how a person having skill in the art might use the claimed polypeptides" and that "no specific biological activity has been identified for the protein set forth in SEQ ID NO:11 other than the fact that the protein may be hyaluronan-binding." *Id.* at page 5 (emphasis added).

Applicants respectfully disagree and traverse.

In particular, Applicants are unclear as to how the Examiner can maintain that the specification does not provide "any biological activity of the polypeptide," while admitting that the specification discloses that BM-HABP binds hyaluronan. *See, e.g.,* specification at page 2, lines 12-13, page 5, lines 33-34 and page 20, lines 28-30. Moreover, Applicants do not understand why the Examiner has disregarded this biological activity throughout her argument. It was well known in the art prior to the filing date of the instant application that hyaluronan is involved in inflammation and arthritis (*see* Oertli *et al*, submitted herewith as reference AK; McCarty, submitted herewith as reference AM; and Uebelhart *et al.*, and references therein, submitted herewith as reference AN). It was also well known that hyaluronan binding receptors were involved in arthritis, inflammation, and malignant processes (see specification page 5, lines 18-28; Naor *et al.*, submitted herewith as reference AO; and Wisniewski *et al.*, and references therein, submitted herewith as reference AP).

Based on the teaching in the specification that the claimed polypeptide binds hyaluronan, and the knowledge of those skilled in the art that hyaluronan and hyaluronan-binding proteins were involved in, *inter alia,* arthritis and inflammation, the specification provides detailed guidance to the skilled artisan to use BM-HABP polynucleotides, polypeptides, agonists, and antagonists for diagnosis, treatment, and prevention of disorders including inflammation and arthritis. *See, e.g.,* specification at page 2, lines 12 to 24. Thus, the specification discloses a biological activity for BM-HABP, and asserts several specific

and substantial utilities based upon that biological activity. In light of the known functions of hyaluronan and hyaluronan binding proteins, these utilities were not only credible, but immediately appreciable to one skilled in the art at the time of filing.

With regard to the Examiner's allegation that BM-HABP cannot be a member of the hyaluronan binding protein family because its disclosed homology to TSG-6 was not close enough, Applicants respectfully disagree. In particular, Applicants disagree with the Examiner's stated figure for percent similarity between TSG-6 (W84087) and BM-HABP. As discussed in the amendments above and shown in Exhibits A and B, BM-HABP and TSG-6 are 31% identical overall, and 43% identical and 58% similar over residues 52-155. As the Examiner did not provide a copy of the alignment cited in the action, Applicants cannot determine how the Examiner's figure of only 14.1% similarity was determined. Regardless, Applicants request a copy of this alignment, and a description of the similarity calculation with the next action.

Moreover, Applicants respectfully contend that the Examiner's argument based on two post-filing date sequences is not supportable. Since these proteins were not known as of the filing date, it is improper to contend that one skilled in the art would rely on their existence as closer homologues to BM-HABP than TSG-6 to disbelieve the asserted utilities for BM-HABP.

Furthermore, not unlike TSG-6, the Q9NRY3 protein (known in the art as FELL, FEEL-2, or STAB2) to which the BM-HABP protein of the instant invention has the highest percent similarity, is also a hyaluronan binding protein (see Politz et al., submitted herewith as reference AI). Politz et al demonstrate that the hyaluronan clearance receptor (which is 94% identical over 353 residues to the BM-HABP protein of the instant invention) is encoded by the *stabilin-2* (STAB2) gene, which is 97% identical over 1059 nucleotides to the BM-HABP nucleotide sequence of the present invention. Politz et al. purified the hyaluronan clearance receptor by hyaluronan-affinity chromatography, indicating the ability of this protein to bind hyaluronan. It is also stated in this manuscript that the STAB2 protein is a member of a novel family of hyaluronan receptor homologues that may play a role in vascular function and inflammatory processes. This further supports the fact that one of skill in the art would find it more likely than not that the BM-HABP protein of the instant invention is, in fact, a member of the hyaluronan binding (HABP) family of proteins and would bind

hyaluronan and be useful for treating, diagnosing or preventing disorders such as inflammation and arthritis as described in the instant specification.

Applicants additionally direct the Examiner's attention to the post-filing date PCT patent application WO01/81544 (submitted herewith as reference AG), titled "Identification and uses of a hyaluronan receptor." This patent application discloses a hyaluronan receptor protein, HARE (HA receptor for endocytosis), comprising an amino acid sequence that is 94% identical over 353 residues to the BM-HABP protein of the present invention. Data presented throughout this application, for example on page 89, lines 5-7 and lines 16-18, indicate that this protein binds hyaluronan, further supporting Applicants' assertion that the BM-HABP protein of the instant invention binds hyaluronan. Applicants submit that this same protein is characterized in the manuscript by Zhou *et al.*, submitted herewith as reference AJ. In this publication, Zhou *et al.* present data confirming the ability of HARE to specifically bind hyaluronan (*see* Zhou *et al.* abstract, Figure 1, and first column of page 340). In particular, these authors identify a putative hyaluronan binding domain located at amino acids 1063-1156 (*see* Zhou *et al.* Figure 6). Of these 94 amino acids, 93 amino acids are identical to those found in the corresponding region of the BM-HABP protein of the instant invention (amino acids 56-149 of SEQ ID NO:11). An alignment of the putative hyaluronan binding domain of human HARE (amino acids 1063-1156) with the corresponding region of BM-HABP of the instant invention (amino acids 56-149 of SEQ ID NO:11) is submitted herewith as Exhibit C.

Applicants point out that subsequently-generated data can be used to support the credibility of a utility asserted in the specification, namely that the BM-HABP protein binds hyaluronan, and could thus be used for the diagnosis, treatment, and prevention of disorders including inflammation and arthritis. *See* Specification at page 20, lines 28-33. As the Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n.19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q. at 370 n.4, emphasis added. *See also* M.P.E.P. § 2107.02(V) and (VII).

Regarding the Examiner's statement that the activities listed in the specification have not been demonstrated, Applicants note that proof of a specific or substantial utility is not the

proper legal standard upon which to evaluate utility. The proper standard is a reasonable correlation, not a statistical certainty, such that one of skill in the art would find the proposed utility more likely than not true (M.P.E.P. 2107.03, page 2100-43, section I). The proper legal standard to judge utility does not rest upon whether data is disclosed. Rather, the standard is whether one of skill in the art, upon reading the entire specification, would find the asserted utilities for the claimed invention an "inherently unbelievable undertaking or involve implausible scientific principle." *In re Brana*, 51 F.3d at 1566. Applicants respectfully submit that, based on the exhibited conserved HA-binding domains of the protein of the instant invention with other HABPs, combined with the post-filing date data discussed above for the STAB2 and HARE proteins which comprise sequences 94% identical to the protein of the instant invention, the present asserted utilities are not implausible to one of skill in the art. Rather, they are clearly and reasonably correlated such that one of skill in the art would find them more likely than not true.

In view of the above, the presently claimed invention possesses specific, substantial, and credible utilities, which constitute patentable utilities under 35 U.S.C. § 101. Because Applicants' assertions of utility are sufficient to satisfy the requirements of 35 U.S.C. § 101, it is respectfully requested that the Examiner's rejection of claims 23-80 under 35 U.S.C. § 101 be reconsidered and withdrawn. If, upon considering the above arguments, the Examiner maintains the utility rejection under §101, Applicants request an interview with Examiner Mitra and Supervisory Patent Examiner Christopher Low. An Interview Request Form PTOL-413A is submitted herewith.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 23-80 remain rejected under 35 U.S.C. first paragraph for alleged lack of enablement. The Federal Circuit and its predecessor determined that the utility requirement of 35 U.S.C. § 101 and the how to use requirement of 35 U.S.C. § 112, first paragraph, have the same basis, *i.e.*, the disclosure of a credible utility. *See In re Brana*, 51 F.3d 1560, 1564, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); *see also* M.P.E.P. § 2107(IV); Utility Examination Guidelines at 1098. As discussed above, the specification teaches specific and well-established utilities of the claimed invention, thereby enabling the skilled artisan to use the

claimed polypeptides. Since the specification contains a detailed description of how to use the claimed polypeptides, and the specification describes specific and immediate utilities for the claimed invention, the claimed invention is enabled. Accordingly, it is respectfully requested that the Examiner's rejection of the claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

The Examiner additionally states on page 8 of Paper No.21 that claimed fragments or sequences having less than 100% identity to SEQ ID NO:11 should have a specific activity such that the fragments or other proteins meeting the structural requirement of the claims will be known by their functional requirements. Applicants are unsure how this requirement relates to enablement, and point out that the specification specifically teaches the use of polypeptide fragments as immunogens to raise antibodies, which does not require biological activity. Nonetheless, solely in the interest of facilitating prosecution, Applicants have amended claims 31, 32, 36, and 37 to recite that the claimed polypeptide "binds hyaluronan." Applicants have additionally amended claims 41-44, 48-51, 55-68 and 72-77 to recite "consisting of." Applicants submit that these latter amended claims do not require a specific activity, as these fragments are precisely defined by their structure. Applicants reserve the right to pursue unamended or canceled subject matter in later, continuing applications. Applicants feel that the above described amendments overcome the Examiner's rejection, and respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application. In the event that this application is not found allowable, Applicants request for an interview with Examiner Mitra and Supervisory Patent Examiner Christopher Low to be scheduled, as indicated by the Applicant Initiated Interview Request form submitted herewith.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an additional extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

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Mark J. Hyman (Reg. No. 46,789)

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Telephone: (240) 314-1224

Enclosures
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